bulk vaccine is 1-4 Lf, the concentration of T per 0.5 ml dose of bulk vaccine does not exceed 10 Lf and the Pa component comprises PT (pertussis toxoid), FHA (filamentous hemagglutinin) and pertactin (69K) wherein the concentration of PT per 0.5 ml dose of bulk vaccine is 2-10 ug; the concentration of FHA per 0.5 ml dose of bulk vaccine is 2-10 ug; and the concentration of 69K is in the range of 0.5 ug to 3 ug per 0.5 ml dose of bulk vaccine.

REMARKS

Claims 1-9 are pending in this application. Claims 1-9 stand rejected. Claim 1 has been amended to more clearly define the present invention. Support for the amended claim can be found on page 2, lines 17-28 of the specification.

Included with this response is a PTO-1449 form.

35 U.S.C. §112, second paragraph

Claims 1 and 3-9 are rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention. The Examiner has noted that claim 1 recites multiple potential ranges for the concentrations of various antigens. Applicants have amended the claim to more clearly define the invention, and to bring it in conformance with U.S. practice.

35 U.S.C. §103(a)

- Claims 1 and 9

Claims 1 and 9 are rejected under 35 U.S.C. §103(a) as being unpatentable over Feery et al. (Ref. V) in view of Edwards et al. (Ref U). The Examiner notes that Feery et al. disclose reduced doses of Diphtheria (2Lf) and Diphtheria (2Lf) + Tetanus (5 Lf) compositions to determine if reduced amounts of diphtheria toxin can be used for vaccinal purposes. Also noted was the fact that Feery et al. do not teach DT in combination with (pertussis) P.

The Examiner explains that Edwards et al. teach DTP vaccines where "diphtheria is generally at a concentration greater than ten, and shows that most vaccines comprising tetanus and diphtheria contain diphtheria at a higher dosage than it does tetanus." Furthermore, the Examiner has noted that Edwards et al. describe a vaccine manufactured by Biocine (BSc-3P) that has all the pertussis components in the concentrations required by

claim 1, but that the diphtheria and tetanus amounts are too high, 25 Lf and 10 Lf, respectively. The Examiner then goes on to conclude that the combination of Feery's et al low dose diphtheria and tetanus with the pertussis components of BSc-3P disclosed by Edwards et al. would have been obvious to one skilled in the art for there is motivation to reduce the amount of diphtheria toxin (Feery et al.) and there would have been a reasonable expectation of success as the lower doses of diphtheria and tetanus disclosed by Feery et al. "were know to work", and the "pertussis vaccine contained in Biocine were known to work".

Applicants respectfully disagree for the following reasons. First of all, Edwards et al. disclose 13 acellular DTPa vaccines with different amounts of antigens as well as various combinations of acellular pertussis antigens. Choosing BSc-3P out of the 13 DTPa vaccines gives the appearance of a hindsight analysis, which is not the standard to determine obviousness. Edwards et al. provide no guidance to select BSc-3P from the other DTPa vaccines in order to make a low dose DTPa vaccine. Feery et al. does not (and could not) provide any additional guidance on this matter, for acellular pertussis vaccines were developed after Feery et al.

Secondly, there would be no reasonable expectation of success. The Examiner is respectfully directed to Table 1 of Edwards et al. where Connaught Laboratories DTPa vaccine, CLL-4F2, is disclosed. CLL-4F2 has less D than found in the BSc-3P vaccine (15Lf verses 25Lf, respectively), less T and the remaining components PT, FHA, 69K, are also within ranges recited in claim 1. However, less D highlights an issue known to those skilled in the art with regards to multiple antigens. Namely, the *combination* of various known antigens, often leads to unpredictability. That is, in some instances, a combination of antigens may lead to an enhanced immune response (i.e., synergy). For the example, the combination of pertussis antigens PT + FHA + 69K leads to an immune response (against pertussis infection) that is greater than one would predict from the individual antigens. More often, however, the combination of antigens leads to a loss in potency of one or more antigens. Sometimes one skilled in the art will add more antigen to boost an immune response, sometimes the skilled man will add less of another antigen (which can mask or "interfere" the immune response to other antigen(s)). Typically for diphtheria toxin, one skilled in the art is aware that the greater the amount of D, the greater the immune response (this is not always true for other antigens, e.g., T). Given that knowledge, one skilled in the

art could not assume, with a reasonable expectation of success, that a lower dose of D in a DTPa combination vaccine would provide effective protection.

As further evidence of Applicants' point, the Examiner is respectfully directed to Edwards et al. again. If one looks at Table 7 and compares the two closest vaccine compositions to the claimed invention (CLL-4F2 and BSc-3P), one sees (i) that decreasing the amount of D, decreases the immune response to that antigen (see Table 7, Antibody to Diphtheria Toxin, Proportion Protected – CLL-4F2 (15Lf of D) = 76.9% verses 92.3% for BSc-3P (25Lf of D). *One conclusion to be drawn is that increasing the amount of D, increases the immune response to D.* This would teach away from the present invention.

Moreover, if one examined all the DTPa vaccines in Table 7, there is no clear correlation between the immune response to D and its dosage in the combination vaccine. In fact, Edwards et al. acknowledged that the clinical data on D was surprising for the DTPa vaccines examined.

> "The variation seen in responses to the diphtheria toxoid component was unexpected . . . acellular vaccines might need to differ from whole-cell vaccines in their diphtheria (and, possibly, tetanus) component to overcome this effect". (see page 555, second column, second paragraph)

Hence, considering the teaching of Edwards et al. as a whole, Applicant respectfully submits that (ii) one skilled in the art could not predict the effect of decreasing the amount of D in a DTPa vaccine, *a priori.*

Either way (i.e., (i) or (ii) above), one of ordinary skill in the art would not have a reasonable expectation of success in developing a new low dose DTPa vaccine by taking the pertussis antigens taught by Edwards et al. in BSc-3P (again, why not choose one of the other 12 DTPa vaccines as well?) and substituting the lower amounts of D (and T) taught by Feery et al. For those reasons, it is respectfully requested that this rejection be withdrawn.

- Claim 2

Claim 2 is rejected under 35 U.S.C. §103(a) as being unpatentable over Feery et al. in view of Edwards. Claim 2 describes a multivalent vaccine comprising the following

constituents at the stated concentrations in a 0.5 ml dosage: PT-8ug, FHA-8ug, 69K-2.5ug, D-2Lf, and T-5Lf.

Feery et al has been cited for a low dose D (2Lf) + T (5Lf) vaccine. Edwards et al. is cited for DTPa vaccines, with pertussis antigens found in the recited ranges of claim 2. However, the amount of D disclosed in all 13 DTPa vaccines of Edwards et al. is higher than claimed by Applicants. The Examiner concludes that one of ordinary skill in the art would have been motivated to combine the pertussis vaccine of the claimed concentrations of Edwards et al. with the Feery et al, diphtheria and tetanus vaccine for reasons previously stated.

Applicants respectfully disagree and note for the reasons stated above, namely (1) that there would be no reasonable expectation of success to combine the cited references given that: (a) there was absolutely no correlation in Edwards et al between the amount of D and the level of protection against Diphtheria infection in DTPa combination vaccines; and (b) Edwards et al found the results surprising as well. Secondly, (2) there was no teaching from the 13 DTPa vaccines disclosed in Edwards et al (Feery et al. is silent on this matter), to select a particular DTPa combination of antigens that was closest to the claimed invention. For those reasons, Applicants respectfully request that this rejection be withdrawn.

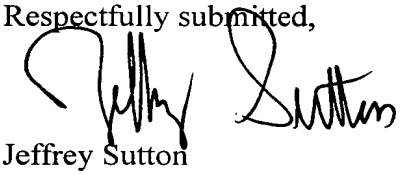
- Claims 1, 3-8 and 9

Claims 1, 3-8 and 9 are rejected under 35 U.S.C. §103(a) as being unpatentable over Feery and Edwards, and further in view of Petre et al (Ref N), and Eckhardt et al. (Ref A). Feery and Edwards are described above. Petre teaches a Hepatitis B vaccine that may be combined with one or more other antigens such as Hepatitis A (HA), D, T, Pa, Hib and polio. Eckhardt et al, teach the desire to combine antigens in order to reduce the number of injections needed to provide protection against various infections.

Applicants note that neither Petre and/or Eckhardt teach a low dose vaccine comprising DTPa. Neither reference teaches a lower amount of D in combination vaccines. Thus for reasons identified above, Applicants respectfully submit that it would not have been obvious to combine the teachings of Feery and Edwards with those of Petre and Eckhardt, for there would be no reasonable expectation of success to arrive at the claimed invention.

In view of the forgoing remarks, Applicants respectfully submit that the instant invention is not obvious over the cited prior art. It is respectfully requested that the outstanding rejections be withdrawn for reasons cited above.

Respectfully submitted,



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"Version with markings to show changes made".

In the claims:

1. (Amended) A vaccine composition comprising diphtheria (D), tetanus (T) and acellular pertussis (Pa) antigens and an adjuvant, wherein [wherein] the concentration of D per 0.5 ml dose of bulk vaccine [does not exceed 5 Lf and is preferably] **is** 1-4 Lf, [more preferably about 2 Lf,] the concentration of T per 0.5 ml dose of bulk vaccine does not exceed 10 Lf [and is preferably 2.5-7.5 Lf, more preferably about 5 Lf] and the Pa component comprises PT (pertussis toxoid), FHA (filamentous hemagglutinin) and pertactin (69K) wherein the concentration of PT per 0.5 ml dose of bulk vaccine [does not exceed 10 ug and is preferably] **is** 2-10 ug[, more preferably about 8 ug]; the concentration of FHA per 0.5 ml dose of bulk vaccine [does not exceed 10 ug and is preferably] **is** 2-10 ug[, more preferably about 8 ug]; and the concentration of 69K [does not exceed 4 micrograms per 0.5 ml dose of bulk vaccine and is preferably] **is** in the range of 0.5 ug to 3 ug[, more preferably approximately 2.5 ug] per 0.5 ml dose of bulk vaccine.